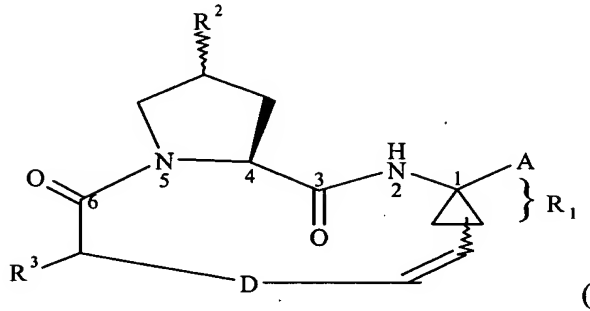
CLAIMS

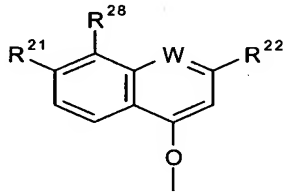
1. A process for the preparation of a macrocyclic compound of formula I



(I)

wherein

R^2 is a hydroxy group, a leaving group or a group of formula II



(II)

W is CH or N,

R^{21} is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, hydroxy, or $N(R^{23})_2$,
wherein each R^{23} is independently H, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^{22} is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} thioalkyl , C_{1-6} alkoxy, C_{3-6} cycloalkoxy, C_{2-7} alkoxyalkyl, C_{3-6} cycloalkyl, $C_{6 \text{ or } 10}$ aryl or Het, wherein Het is a five-, six-, or seven-membered saturated or unsaturated heterocycle containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur;
said cycloalkyl, aryl or Het being substituted with R^{24}, wherein

R^{24} is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, NO_2, $N(R^{25})_2$, NH-C(O)-R^{25}; or NH-C(O)-NH-R^{25}, wherein each R^{25} is independently: H, C_{1-6} alkyl or C_{3-6} cycloalkyl; or

R^{24} is NH-C(O)-OR^{26} wherein R^{26} is C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^{28} is H, halo or C_{1-6} alkyl,

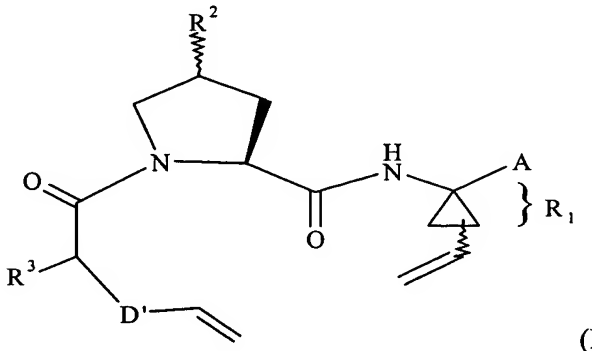
R^3 is hydroxy, NH_2, or a group of formula - NH-R^{31}, wherein R^{31} is $C_{6 \text{ or } 10}$ aryl, heteroaryl, -C(O)-R^{32}, –C(O)-NHR^{32} or –C(O)-OR^{32},
wherein R^{32} is C_{1-6} alkyl or C_{3-6} cycloalkyl;

D is a 3 to 7-atom saturated alkylene chain; and

A is an amide of formula –C(O)-NH-R^5, wherein R^5 is selected from the group consisting of: C_{1-8} alkyl, C_{3-6} cycloalkyl, $C_{6 \text{ or } 10}$ aryl, C_{7-16} aralkyl; and SO_2R^{5A} wherein R^{5A} is C_{1-8} alkyl, C_{3-7} cycloalkyl or {C_{1-6} alkyl-C_{3-7} cycloalkyl }, or

A is a carboxylic acid or a pharmaceutically acceptable salt or ester thereof;

which process comprises subjecting a diene compound of formula III

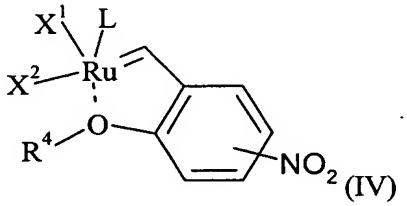


(III)

wherein R^2, R^3 and A are as defined hereinbefore; and

D' represents a 3 to 7-atom saturated alkylene chain;

to a metathesis cyclization reaction in the presence of a ruthenium catalyst of formula IV:



(IV)

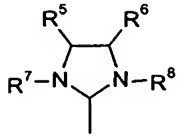
wherein

X^1 and X^2 each independently represent an anionic ligand;

L represents a neutral electron donor ligand; and

R^4 represents a C_{1-6} alkyl, C_{2-6} alkenyl or C_{6-12} aryl-C_{1-6} alkyl group.

2. A process according to claim 1 for the preparation of a macrocyclic compound of formula I, wherein L of formula IV is a trihydrocarbylphosphine group or a group of formula



wherein

R^5 and R^6 each independently represent a hydrogen atom or a C_{1-6} alkyl, C_{2-6} alkenyl, C_{6-12} aryl or C_{6-12} aryl-C_{1-6} alkyl group; or

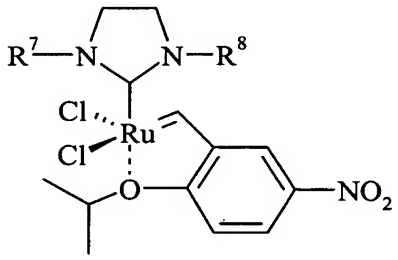
R^5 and R^6 together form a double bond; and

R^7 and R^8 each independently represent a hydrogen atom or a C_{1-6} alkyl, C_{2-6} alkenyl, C_{6-12} aryl or C_{6-12} aryl-C_{1-6} alkyl group, each optionally substituted by one, two or three groups independently selected from halogen, C_{1-6}alkyl and C_{1-6}alkoxy;

X^1 and X^2 each independently represent a halogen atom; and

R^4 represents a C_{1-6} alkyl group.

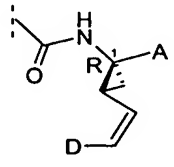
3. A process according to claim 1 for the preparation of a macrocyclic compound of formula I, wherein the ruthenium catalyst is a compound of formula IVA



IVA

wherein R^7 and R^8 represent a mesityl group.

4. A process according to claim 1 for the preparation of a macrocyclic compound of formula I, wherein R_1 moiety is a group of formula (i)



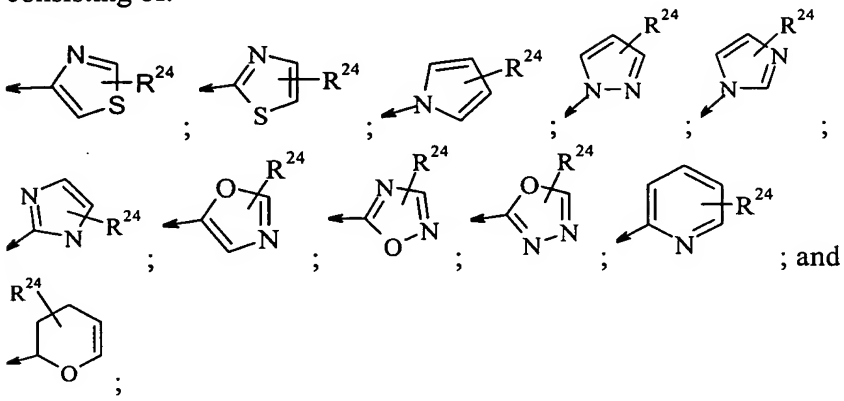
(i);

R^2 is a group of formula II,; and

W is N;

R^{21} is H, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, chloro;

R^{22} is H, C_{1-6} thioalkyl, C_{1-6} alkoxy, phenyl or Het selected from the group consisting of:



wherein R^{24} is H, C_{1-6} alkyl, NH-R^{25}, NH-C(O)-R^{25}; NH-C(O)-NH-R^{25}, wherein each R^{25} is independently: H, C_{1-6} alkyl, or C_{3-6} cycloalkyl; or NH-C(O)-OR^{26}, wherein R^{26} is C_{1-6} alkyl;

R^{28} is H, bromine or methyl; or

R^2 is a leaving group of formula $-OSO_2-R^{27}$, wherein R^{27} is selected from p-toluyl, p-bromophenyl, p-nitrophenyl, methyl, trifluoromethyl, perfluorobutyl and 2,2,2-trifluoroethyl.

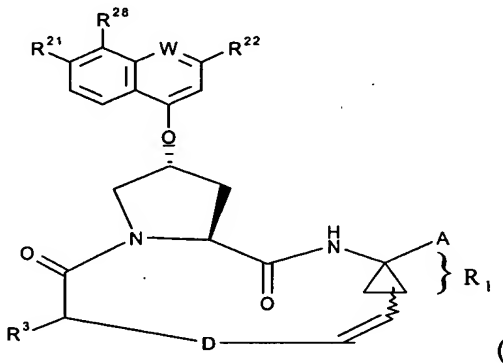
5. A process according to claim 1 for the preparation of a macrocyclic compound of formula I, wherein metathesis reaction is carried out in the presence of a diluent in a temperature range from 40 to 120 °C.

6. A process according to claim 1 for the preparation of a macrocyclic compound of formula I, wherein metathesis reaction is carried out in the presence of a diluent selected from alkanes, aromatic hydrocarbons, and chlorinated hydrocarbons.

7. A process according to claim 1 for the preparation of a macrocyclic compound of formula I, wherein the molar ratio of the diene compound of formula III to catalyst of formula IV ranges from 1000 : 1 to 100 : 1.

8. A process according to claim 1 for the preparation of a macrocyclic compound of formula I, wherein the ratio of the diene compound of formula III to diluent ranges from 1 : 400 by weight to 1 : 25 by weight.

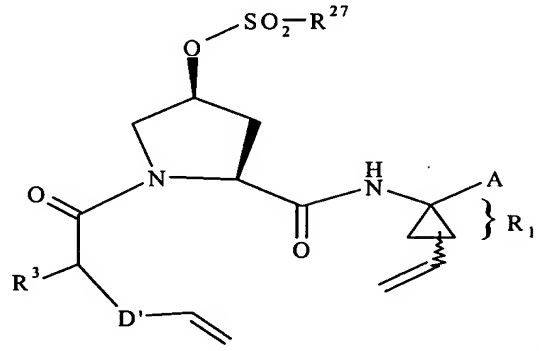
9. A process for the preparation of a macrocyclic compound of formula I



(I)

wherein R^3, R^{21}, R^{22}, R^{28}, W, A and D are as defined in claim 1, which comprises the following steps:

(i) cyclizing a diene compound of formula III

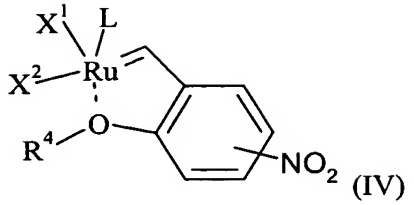


(III)

wherein R^3 and A are as defined in claim 1, and R^{27} is selected from p-toluyl, p-bromophenyl, p-nitrophenyl, methyl, trifluoromethyl, perfluorobutyl and 2,2,2-trifluoroethyl; and

D' represents a 3 to 7-atom saturated alkylene chain;

in the presence of the ruthenium catalyst of formula IV:



(IV)

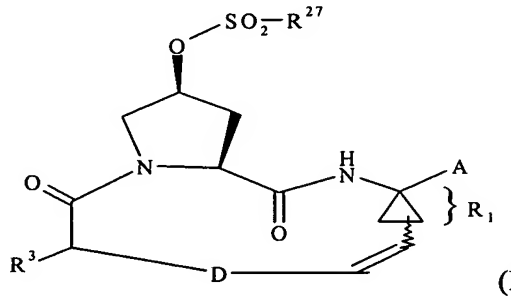
wherein

X^1 and X^2 each independently represent an anionic ligand;

L represents a neutral electron donor ligand; and

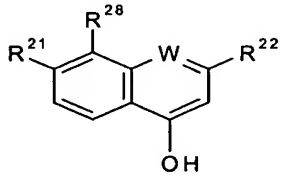
R^4 represents a C_{1-6} alkyl, C_{2-6} alkenyl or C_{6-12} aryl-C_{1-6} alkyl group; and

(ii) reacting the resulting macrocyclic compound of formula I,



(I)

wherein A, R^3 and D are as defined in claim 1 , and R^{27} is as defined above in step (i), with a compound of formula V,



(V)

wherein R^{21}, R^{22}, R^{28} and W are as defined in claim 1.